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Improved Antibiotic-Impregnated Catheters with Extended-Spectrum Activity against Resistant Bacteria and Fungi

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Minocycline-rifampin-impregnated central venous catheters (M/R CVCs) have been shown to be efficacious in reducing catheter-related bloodstream infections (CRBSI) and inhibiting the biofilm adherence of resistant Gram-positive and Gram-negative pathogens, with the exception of *Pseudomonas aeruginosa* and *Candida* spp. To expand the spectrum of antimicrobial activity, a novel second-generation M/R catheter was developed by adding chlorhexidine (CHX-M/R). CVCs and peripherally inserted central catheters (PICCs) were impregnated with CHX-M/R and compared with first-generation M/R catheters, CHX-silver sulfadiazine-treated CVCs (CHX/SS-CVCs), chlorhexidine-treated PICCs, and uncoated catheters. A biofilm catheter colonization model was used to assess the efficacy of catheters against methicillin-resistant *Staphylococcus aureus* (MRSA), vancomycin-resistant *Enterococcus faecium* (VRE), *P. aeruginosa*, *Candida albicans*, and *Candida glabrata*. CHX-M/R-impregnated CVCs were the only antimicrobial catheters that completely inhibited the biofilm colonization of all resistant bacterial and fungal organisms tested at all time intervals, and they were significantly superior to uncoated catheters (all *P* values were ≤0.003). Furthermore, CHX-M/R-coated CVCs had a significantly more effective and prolonged (up to 3 weeks) antimicrobial activity against MRSA and *P. aeruginosa* than M/R, CHX/SS, and uncoated CVCs ($P < 0.0001$). Similarly, CHX-M/R-coated PICCs were also superior to M/R-coated and CHX-coated PICCs in preventing biofilms of MRSA, VRE, *P. aeruginosa*, and *Candida* species (P value = 0.003 for all). Our study shows that novel CHX-M/R-coated catheters have unique properties in completely inhibiting biofilm colonization of MRSA, VRE, *P. aeruginosa*, and fungi in a manner superior to that of M/R- and chlorhexidine-treated catheters.

Central venous catheters (CVCs) have become essential devices in the care of critically ill patients, cancer patients, and those requiring hemodialysis or total parenteral nutrition (TPN) (17). Even though these catheters have become the lifeline for such seriously ill patients, they are not without risks. Their use has been associated with a large range of complications, the most serious and frequent of which is central line-associated bloodstream infection (CLABSI) (10, 13). It is estimated that more than 300,000 episodes of CLABSI occur yearly in the United States (17). In critically ill patients, CVCs have been shown to be the source of 87% of bloodstream infections occurring in the intensive care unit (ICU) (22), resulting in increases in hospital stay ranging from 7 to 11.9 days (14, 17).

Coating or impregnating the external and internal surfaces of CVCs with antimicrobial agents (referred to as antimicrobial CVCs) helped to markedly reduce the risk of CLABSI, and their use has become the standard of care (11, 21). A systematic review of 34 studies using antimicrobial CVCs has shown that such antimicrobial devices result in significant reductions in the rate of CLABSI compared to that observed with uncoated standard CVCs (21). Another meta-analysis of 38 randomized controlled trials has shown that antimicrobial CVCs are safe and have a strongly significant therapeutic effect in reducing CLABSI, without any substantial risk for emergence of resistance (11).

The two most effective antimicrobial CVCs that are recommended by CDC guidelines are those coated with minocycline-rifampin (M/R) or those coated with chlorhexidine and silver sulfadiazine (CHX/SS) (11, 13, 21). First-generation CHX/SS-coated CVCs have been associated with a short antimicrobial durability of around 7 days and were 12-fold less effective than M/R catheters in a large multicenter randomized trial (5). CVCs impregnated with M/R have been associated with prolonged antimicrobial durability *in situ*, for around 50 days (4). Furthermore, M/R catheters were found to have superior antiadherence activity and prolonged antimicrobial durability compared to second-generation CHX/SS-coated CVCs against vancomycin-resistant *Staphylococcus aureus* and multidrug-resistant (MDR) Gram-negative organisms other than *Pseudomonas* (18). Although M/R catheters have excellent activity against staphylococci and most of the Gram-negative bacilli (18), they lack activity against *Pseudomonas aeruginosa* (which contributes to around 3 to 5% of CLABSI) and *Candida* spp. (which contribute up to 12% of all CLABSI) (18). Therefore, our group has developed a novel antimicrobial CVC that is coated with a combination of chlorhexidine and minocycline-rifampin (CHX-M/R) by a proprietary saturation method. Preliminary *in vitro* studies have shown that CHX-M/R-coated CVCs provide better protection against methicillin-resistant *Staphylococcus aureus* (MRSA), *P. aeruginosa*, and *Candida* sp. than M/R-coated CVCs (19) and provide more prolonged antimicrobial durability than CHX/SS and M/R catheters. In the current study, we compared the *in vitro* activities and durabilities of the traditional FDA-approved M/R- or CHX/SS-coated CVCs and M/R- or CHX-coated peripherally inserted central catheters

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(PICCs) to those of the novel CHX-M/R catheters in inhibiting the biofilm colonization of MRSA, vancomycin-resistant *Enterococcus faecium* (VRE), *P. aeruginosa*, and *Candida* species.

MATERIALS AND METHODS

Impregnation of CVCs and PICCs with CHX-M/R. Experimental CHX-M/R CVCs and PICCs were produced by impregnating polyurethane catheters (Cook Medical, Bloomington, IN) with a novel combination of CHX-M/R for 4 h, based on a modification of a proprietary method (I. Raad, patent pending). Briefly, catheter segments (4 cm in length) were impregnated first in chlorhexidine solution (40 mg/ml) for 4 h and then continued to be impregnated with a mixture of minocycline (15 mg/ml) and rifampin (30 mg/ml) for an additional 1 h. After impregnation, catheters were air flushed to remove any excess coating solution from the lumens of the catheters, dried at 55°C overnight, washed with water, and dried again. Commercially available uncoated polyurethane 7-Fr triple-lumen CVCs, M/R-CVCs, double-lumen M/R PICCs (Cook Medical, Bloomington, IN), CHX/SS-CVCs (Arrowgard Blue Plus; Arrow International, Inc., Reading, PA), and CHX PICCs (Chloragard; Arrow International, Inc., Reading, PA) were also tested as comparators and controls.

***In vitro* biofilm colonization.** Following a modified Kuhn's model of biofilm colonization (8, 12), 1-cm-long segments of uncoated control catheters and the above-mentioned coated catheters (CVCs and PICCs) were tested in triplicate for inhibition of biofilm formation by MRSA strain 4798, VRE strain 3238, *P. aeruginosa* strain 4689, *Candida albicans* strain 009-3072, and *Candida glabrata*. The catheters were placed into sterile 24-well tissue culture plates containing 1 ml of human donor plasma to enhance the formation and binding of blood proteins and were incubated for 24 h at 37°C. The plasma was then replaced with 5.0×10^5 cells of various organisms in Mueller-Hinton broth, and the plates were incubated for an additional 24 h. After incubation, the microbial inoculum was discarded and segments were washed with shaking for 30 min in 1 ml of 0.9% sterile saline. The segments were then removed with sterile sticks, placed in 5 ml of 0.9% saline, and sonicated for 15 min at 40 kHz. After sonication, each sample was vortexed for 5 s, and 100 μl of liquid from each segment was serially diluted and spread onto Trypticase soy agar plus 5% sheep blood for quantitative culture of bacterial species or onto Sabouraud dextrose agar for culture of yeast species. Plates were incubated inverted at 37°C for 24 h and then counted for colony growth. Experiments were repeated twice ($n = 6$ segments in total).

Durability testing. To test the durability of prolonged inhibition of MRSA, *P. aeruginosa*, *C. albicans*, and *C. glabrata* biofilm formation, uncoated control, M/R, CHX-M/R, and CHX-SS CVC segments were tested at baseline (24 h) and at 1, 2, and 3 weeks. In order to simulate biological conditions for durability testing, six segments of each CVC type were immersed in 10 ml of serum and incubated at 37°C for the duration of testing. At each 1-week interval, segments were removed from serum and tested using the biofilm colonization model as described above (8, 12).

Testing of shelf life of CHX-M/R CVCs and PICCs. To determine if CHX-M/R-coated CVC and PICC segments would remain active, catheters were stored at room temperature (25°C) for 1 year and then tested to determine the real-time shelf life of their antimicrobial activity. After 1 year, CVC and PICC segments were tested for biofilm formation by MRSA and *P. aeruginosa* for 24 h, using the biofilm colonization model as described before (8, 12).

Statistical methods. CFU were compared by the Kruskal-Wallis test for each organism. If a significant result was detected for the test, we used Wilcoxon rank sum tests for pairwise comparisons. The α levels of the *post hoc* pairwise comparisons were adjusted using a sequential Bonferroni adjustment to control type I error. For the study of durability of prolonged biofilm inhibition, two-way nonparametric analysis of variance (ANOVA) was used to compare CFU among different types of catheters. All tests were two-sided, with a significance level of 0.05. The statistical analyses were performed using SAS, version 9.1 (SAS Institute Inc., Cary, NC).

RESULTS

Baseline activity of antimicrobial CVCs. CHX-M/R-impregnated CVCs demonstrated an antiadherence activity against all the organisms tested and were significantly superior to uncoated and M/R-coated CVCs, with a complete inhibition of biofilm formation by MRSA, *P. aeruginosa*, *C. albicans*, and *C. glabrata* (all *P* values were ≤ 0.03) (Fig. 1). Furthermore, the novel CHX-M/R combination was significantly more effective than CHX/SS in inhibiting the biofilm growth of *P. aeruginosa* ($P = 0.01$).

In vitro adherence of M/R-impregnated CVCs showed a significant reduction (5 log) in the viable biofilm colony counts of MRSA (median [range], 4.3×10^2 [0 to 8×10^2] versus 1.9×10^7 [1.5×10^7 to 2.6×10^7]; $P = 0.005$) and *P. aeruginosa* (median [range], 7.0×10^2 [0 to 4.3×10^3] versus 6.5×10^7 [1.3×10^7 to 1.9×10^9]; $P = 0.005$) compared to those with uncoated control CVCs (Fig. 1). Biofilm formation of *C. albicans* and *C. glabrata* was not inhibited by M/R CVCs and showed no difference in activity from that in uncoated CVCs ($P = 0.81$) (Fig. 1). The CHX/SS CVCs significantly reduced the biofilm colonization of MRSA (median [range], 0 [0 to 3.9×10^3] versus 1.9×10^7 [1.5×10^7 to 2.6×10^7]; $P = 0.004$), *C. albicans* (median, 0 versus 2.9×10^4; $P = 0.003$), *C. glabrata* (median, 0 versus 1.9×10^4; $P = 0.003$), and *P. aeruginosa* (median [range], 2.8×10^3 [0 to 4.6×10^3] versus 6.5×10^7 [1.3×10^7 to 1.9×10^9]; $P = 0.005$) compared to uncoated CVCs (Fig. 1). No significant difference in the biofilm colonization of MRSA and *P. aeruginosa* was found between M/R and CHX/SS CVCs (*P* values were not significant); however, there was a significant difference in biofilm colonization of *C. albicans* and *C. glabrata* between M/R and CHX/SS CVCs ($P = 0.003$).

Baseline activity of antimicrobial PICCs. Biofilm colonization of all organisms tested was completely inhibited by CHX-M/R PICCs ($P = 0.003$ for all), in a manner superior to that for all other (M/R, CHX, and uncoated) PICCs tested against MRSA, VRE, *P. aeruginosa*, and *Candida* species (Fig. 2). M/R and CHX PICCs showed a trend toward significant differences compared with CHX-M/R against biofilm growth of MRSA ($P = 0.07$). M/R-coated PICCs and CHX PICCs showed a significant decrease in biofilm colonization of MRSA (6-log reduction) and a 3-log reduction in VRE versus uncoated controls ($P = 0.005$) (Fig. 2). For *P. aeruginosa*, there was a 1-log reduction in biofilm colonization for both M/R and CHX PICCs compared to controls ($P = 0.01$), but there was no difference between M/R and control PICCs ($P = 0.75$). For *C. albicans* and *C. glabrata*, there was a 2-log reduction for both M/R-coated and CHX PICCs compared to controls ($P \leq 0.008$) (Fig. 2).

Durability of antimicrobial-coated CVCs. CHX-M/R CVCs were the only antimicrobial CVCs that completely inhibited biofilm growth of the resistant bacteria and fungi at all intervals during the testing period.

CHX-M/R-coated CVC segments had a significantly longer antimicrobial durability against MRSA (Fig. 3A) and *P. aeruginosa* (Fig. 3B) than the M/R, CHX-SS, and uncoated CVCs (all *P* values were <0.0001) during the testing period. Furthermore, CHX-M/R and CHX/SS CVCs also had more effective antimicrobial durability against *C. albicans* (Fig. 4A) and *C. glabrata* (Fig. 4B) than M/R and uncoated CVCs (all *P* values were <0.0001) over the 3-week testing period.

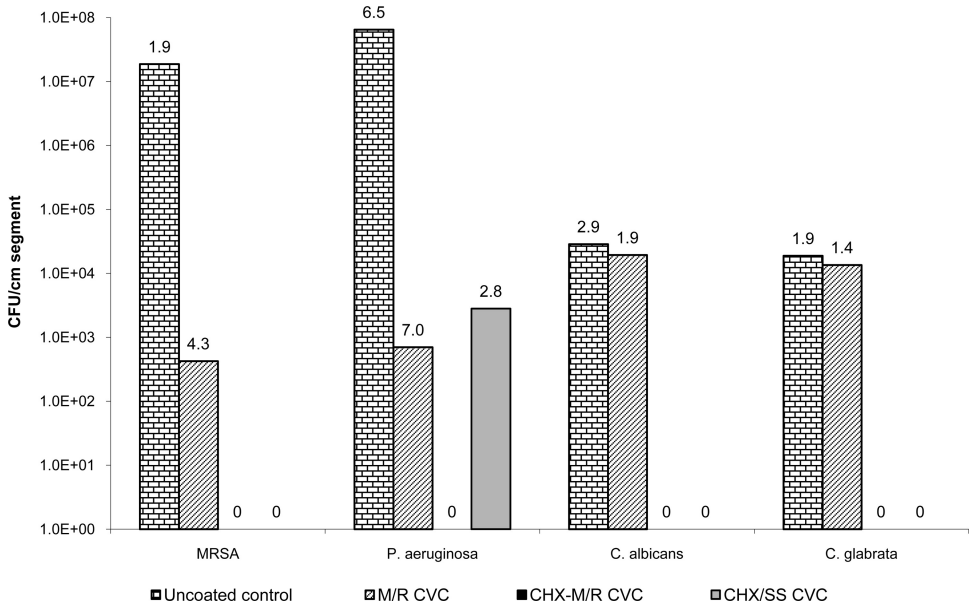

FIG 1 *In vitro* biofilm adherence of various microorganisms to different antimicrobials coating CVC surfaces after 24 h of biofilm formation. M/R, minocycline and rifampin; CHX, chlorhexidine; SS, silver sulfadiazine; NS, not statistically significant. *P* values for MRSA and *P. aeruginosa* were as follows: control versus M/R CVC, $P = 0.005$; control versus CHX-M/R CVC, $P = 0.003$; control versus CHX/SS CVC, $P = 0.004$; CHX-M/R CVC versus M/R CVC, $P = 0.03$; and CHX-M/R CVC versus CHX/SS CVC, $P =$ NS. *P* values for *C. albicans* and *C. glabrata* were as follows: control versus M/R CVC, $P =$ NS; control versus CHX-M/R CVC, $P = 0.003$; control versus CHX/SS CVC, $P = 0.003$; CHX-M/R CVC versus M/R CVC, $P = 0.003$; and CHX-M/R CVC versus CHX/SS CVC, $P = 0.003$.

Shelf life of CHX-M/R CVCs and PICCs. After 1 year of real-time shelf life, both CHX-M/R CVCs and PICCs continued to inhibit biofilm growth of MRSA (Fig. 5A) and *P. aeruginosa* (Fig. 5B) compared to uncoated catheters ($P \leq 0.004$); hence, the antimicrobial activity remained unaltered compared to that of freshly impregnated catheters.

DISCUSSION

The most recent CDC guidelines recommended two antimicrobial CVCs that were shown to be highly effective in preventing biofilm colonization and highly efficacious in preventing CLABSI through multiple prospective randomized trials (13). These two FDA-approved antimicrobial CVCs consisted of M/R-coated

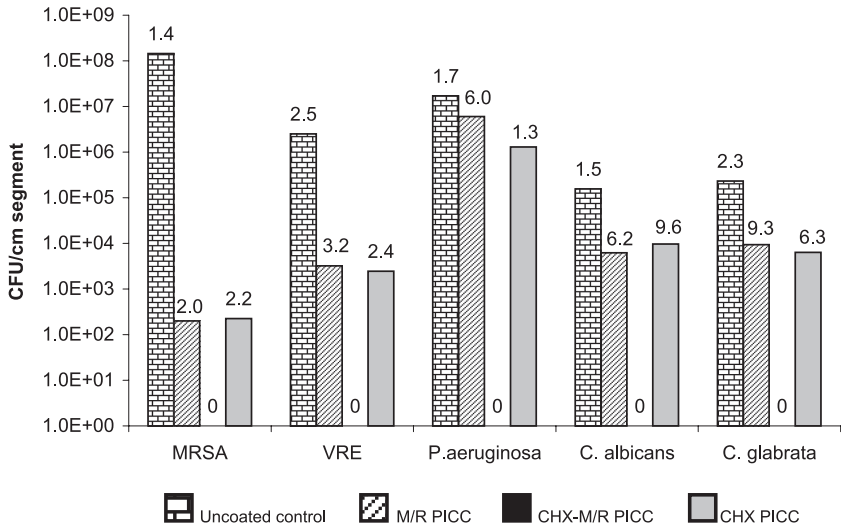

FIG 2 Biofilm colonization of various microorganisms on different antimicrobial-coated PICC surfaces after 24 h of biofilm formation. M/R, minocycline and rifampin; CHX, chlorhexidine; NS, not statistically significant. *P* values for MRSA were as follows: control versus M/R PICC, $P = 0.005$; control versus CHX-M/R PICC, $P = 0.003$; control versus CHX PICC, $P = 0.005$; CHX-M/R PICC versus M/R PICC, $P = 0.07$; and CHX-M/R PICC versus CHX PICC, $P = 0.07$. *P* values for VRE were as follows: control versus M/R PICC, $P = 0.005$; control versus CHX-M/R PICC, $P = 0.004$; control versus CHX PICC, $P = 0.005$; CHX-M/R PICC versus M/R PICC, $P = 0.004$; and CHX-M/R PICC versus CHX PICC, $P = 0.01$. *P* values for *P. aeruginosa* were as follows: control versus M/R PICC, $P =$ NS; control versus CHX-M/R PICC, $P = 0.003$; control versus CHX PICC, $P = 0.01$; CHX-M/R PICC versus M/R PICC, $P = 0.003$; and CHX-M/R PICC versus CHX PICC, $P = 0.008$. *P* values for *C. albicans* and *C. glabrata* were as follows: control versus M/R PICC, $P < 0.01$; control versus CHX-M/R PICC, $P = 0.003$; control versus CHX PICC, $P = 0.005$; CHX-M/R PICC versus M/R PICC, $P = 0.003$; and CHX-M/R PICC versus CHX PICC, $P =$ NS.

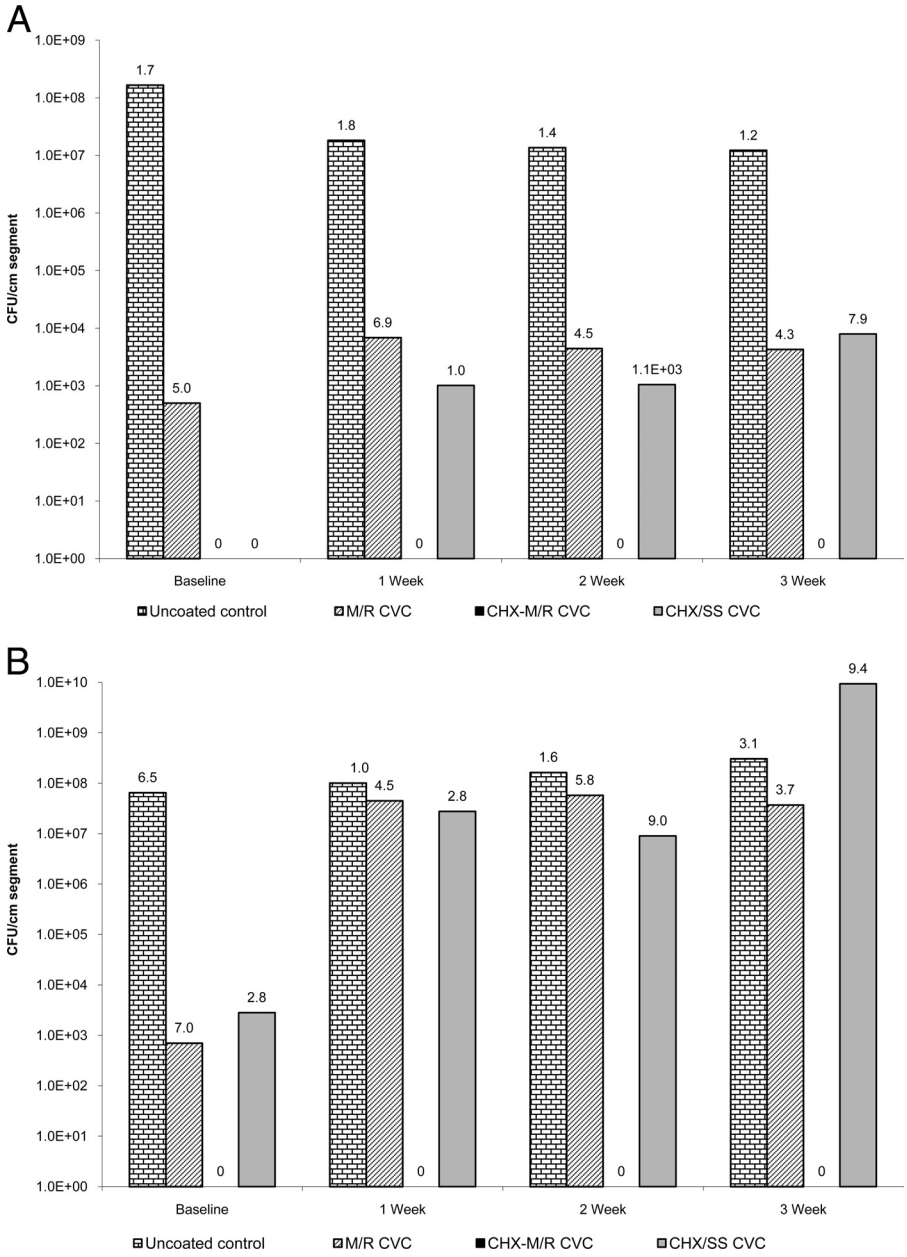

FIG 3 Efficacy against bacteria and durability for up to 3 weeks for different antimicrobials coating CVCs. M/R, minocycline and rifampin; CHX, chlorhexidine; SS, silver sulfadiazine. (A) Methicillin-resistant *Staphylococcus aureus*; (B) *Pseudomonas aeruginosa*. CHX-M/R CVCs were more durable and efficacious than M/R CVCs ($P < 0.0001$), and M/R CVCs were more so than the controls ($P < 0.0001$). CHX-M/R CVCs were more durable and efficacious than CHX/SS CVCs ($P < 0.0001$), and CHX/SS CVCs were more so than the controls ($P < 0.0001$).

CVCs and those treated with CHX/SS. According to our data, we have demonstrated that a novel antimicrobial catheter that combines the same active antimicrobial ingredients (chlorhexidine and minocycline-rifampin) used in the two prior traditional antimicrobial CVCs is highly and uniquely effective in completely preventing the biofilm colonization of MRSA, multidrug-resistant *P. aeruginosa*, and *Candida* sp. organisms that cause CLABSI. In addition, the antimicrobial activity and durability of this novel antimicrobial CVC (CHX/MR) were significantly superior to those of the traditional M/R and CHX/SS CVCs in preventing biofilm colonization of MRSA and *P. aeruginosa* after 3 weeks of immersion in serum. Furthermore, the extended-spectrum CHX-M/R PICC was superior to CHX PICCs in preventing biofilm formation of two *Candida* species in addition to the bacteria tested. Finally, the novel CHX-M/R CVC and PICC retained antimicrobial activity after 1 year of shelf life.

Preventive measures such as a bundle of aseptic procedures during insertion have been instituted to reduce the risk of CLABSI. This bundle of aseptic procedures has become the standard of care in the United States and is currently recommended through the CDC guidelines (13). This recommendation is based largely on a multicenter prospective crossover study in Michigan,

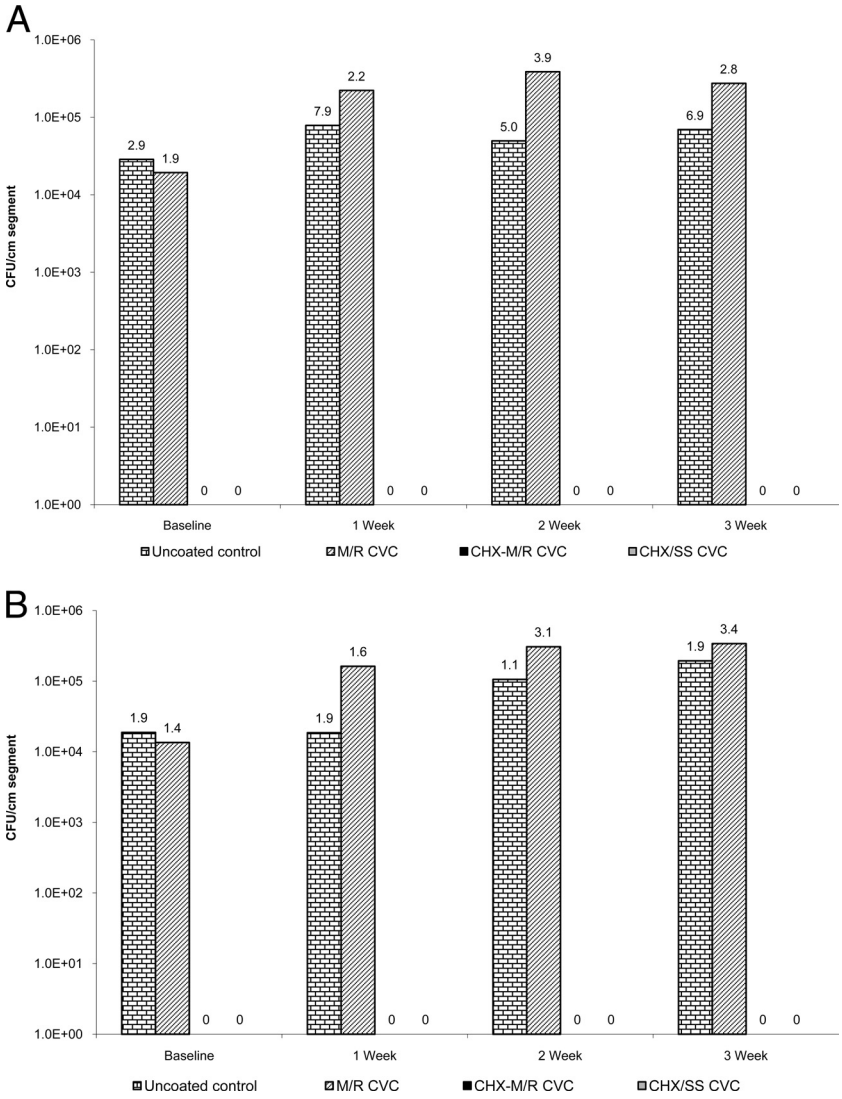

FIG 4 Efficacy against fungi and durability for up to 3 weeks for different antimicrobials coating CVCs. M/R, minocycline and rifampin; CHX, chlorhexidine; SS, silver sulfadiazine. (A) *Candida albicans*; (B) *Candida glabrata*. CHX-M/R CVCs were more durable and efficacious than the controls ($P < 0.0001$), and CHX/SS CVCs were also more durable and efficacious than the controls ($P < 0.0001$). The controls were more durable and efficacious than M/R CVCs ($P = 0.002$).

conducted by Pronovost et al., that demonstrated that the use of a bundle of aseptic procedures (referred to as "the bundle")—consisting of maximal sterile barriers, hand washing, and cleaning of the skin insertion site with chlorhexidine, as well as avoidance of the femoral vein insertion site and removal of unnecessary catheters—resulted in a significant decrease in the incidence of CLABSI in critically ill patients (15). In the Pronovost study, the rate of CLABSI decreased from the baseline rate of 7.7 cases per 1,000 catheter days to 1.4 cases per 1,000 catheter days 6 to 12 months after the introduction of the aseptic procedure bundle (15). However, the Pronovost study has limitations due to its crossover design, the lack of assessment of compliance, the lack of assessment of confounding variables (such as the introduction of antimicrobial-coated catheters), and the poor definitions of bacteremia and catheter-related bloodstream infections.

A more recent and larger study by Furuya et al. that involved 250 National Healthcare Safety Network (NHSN) hospitals demonstrated the difficulty of compliance with all the elements of the bundle of aseptic procedures (6). In this large study, only 38% of hospitals that monitored compliance reported compliance with all components of the bundle. Furthermore, compliance with all bundle elements was not necessary to show a decrease in CLABSI, and the CLABSI rates in the study ranged from 1.69 to 2.7 cases per 1,000 catheter days, irrespective of the degree of compliance.

The CDC, as well as the Center for Medical Services, has called for zero tolerance for CLABSI because of the seriousness of catheter-related bloodstream infections, which are thought to be completely preventable (20). Based on all of the studies that have used the bundle, the level of CLABSI could not be reduced below 1.4 cases/1,000 catheter days in critically ill patients (6, 15). However, there are hints in the literature that if the aseptic bundle is used with a combination of antimicrobial CVCs, the rate of CLABSI could be lowered to a level below 0.5 case/1,000 catheter days, to as low as 0.25 case/1,000 catheter days (9, 23).

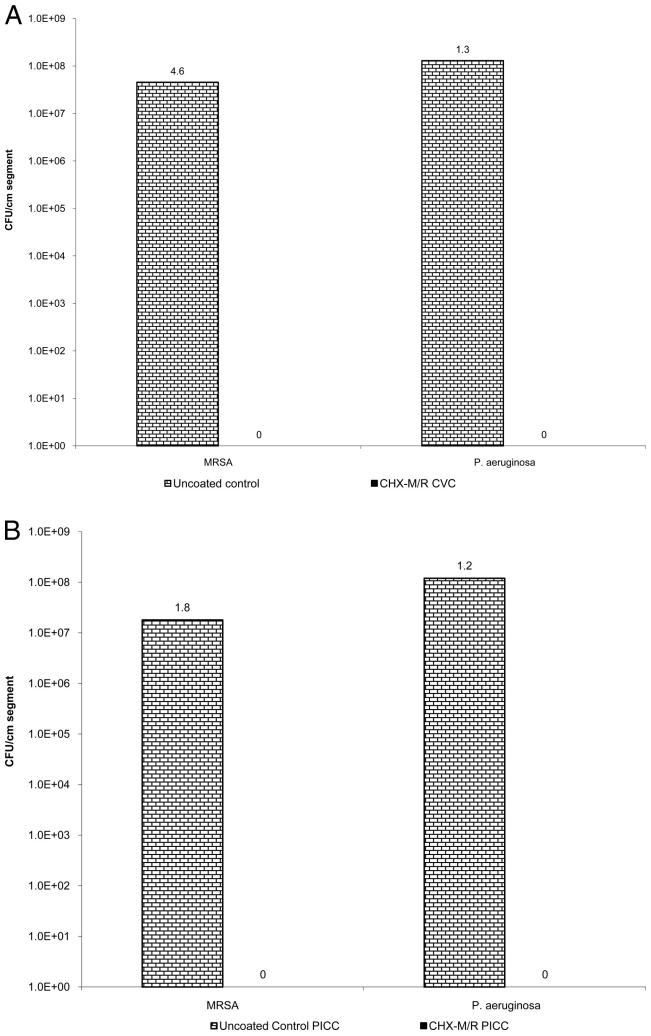

FIG 5 Shelf life of CHX-M/R central venous catheter (A) and peripherally inserted central catheter (B) at room temperature. The catheters were tested against methicillin-resistant *Staphylococcus aureus* (MRSA) and *Pseudomonas aeruginosa* by determining the amounts of biofilm colonization. M/R, minocycline and rifampin; CHX, chlorhexidine.

Based on the data derived from this study, it is possible that highly effective, novel antimicrobial CVCs such as the CHX-M/R catheter, combined with the aseptic technique bundle, might bring the CLABSI rate to a level that is as close as possible to zero.

Using an *in vitro* biofilm colonization model, we tested the antimicrobial activity and durability of M/R-, CHX/SS-, and CHX-M/R-coated CVCs against MRSA. MRSA represents the most resistant and virulent form of staphylococci. Staphylococci and Gram-positive organisms are the cause of 60% to 70% of CLABSI (5, 10). A large multicenter study conducted by the CDC that evaluated CLABSI from 1997 to 2007 determined that the majority (61%) of the 4,088 *S. aureus* CLABSI nationwide were caused by MRSA (3). Traditionally, M/R catheters have been shown to be significantly more effective at preventing biofilm colonization of staphylococci than CHX/SS catheters, with superior antimicrobial durability (18). Because the majority of CLABSI are caused by staphylococci, these prior findings could have contributed to the clinical superiority of the M/R CVC over the first-generation CHX/SS-coated CVC in a multicenter clinical trial (16). In the current study, M/R-coated CVCs were significantly superior to control uncoated CVCs in preventing biofilm colonization of MRSA. However, the M/R-coated CVC showed equivalent antimicrobial activity and durability to those of the second-generation CHX/SS CVC, even though it showed superior activity in previous studies. On the other hand, the CHX-M/R CVC showed superior antimicrobial activity and durability to those of the two other traditional CVCs, M/R- and CHX/SS-coated CVCs, with complete inhibition of biofilm colonization of MRSA over a 3-week period of incubation in serum.

A multidrug-resistant *P. aeruginosa* strain was chosen to be tested because it reflects the most resistant and virulent form of Gram-negative bacteria, which contribute to 17% to 24% of all CLABSI. Traditionally, the M/R CVC showed little activity against MDR *P. aeruginosa* (8), but it showed superior activity compared to the CHX/SS-coated CVC in preventing the adherence of biofilm colonies of other common Gram-negative bacteria, such as *Stenotrophomonas maltophilia* and *Acinetobacter* (18). However, in the current study, both the M/R and CHX/SS CVCs showed limited equivalent activity and durability against *P. aeruginosa*, which were superior to those of uncoated catheters but significantly inferior to those of the CHX-M/R CVC. The M/R and CHX/SS CVC durability was limited to some baseline activity against *P. aeruginosa*, which was lost in a week given the resistant nature of this organism.

Finally, catheter-related candidemia has been on the rise, particularly with the emergence of fluconazole-resistant *Candida glabrata* as one of the leading causes of health care-associated candidemia nationwide (10). The use of a CVC has been shown to be an independent risk factor for candidemia by multivariate analysis (1, 2), and the attributable mortality of health care-associated candidemia has been reported to be in the range of 38% to 49% (7). *Candida* species contribute to around 10% to 15% of all CLABSI. Other studies have shown that the M/R and CHX/SS CVCs failed to completely inhibit the biofilm colonization of *Candida* organisms on the surfaces of the catheters (8). However, according to our data, the novel CHX-M/R CVC completely inhibits the biofilm colonization of *Candida*, even after 3 weeks of immersion and incubation in serum, and it was shown to have superior antimicrobial activity and durability compared to the M/R CVC, as well as the CHX/SS-coated CVC, in preventing the biofilm colonization of both *C. albicans* and *C. glabrata*.

Conclusions. The novel extended-spectrum CVC and PICC impregnated with CHX-M/R were shown to be superior to other traditional antimicrobial CVCs and PICCs currently approved by the FDA and recommended by the CDC for preventing the biofilm colonization of resistant pathogens that often cause CLABSI. The CHX-M/R CVC was significantly more efficacious in completely inhibiting the biofilm colonization of resistant bacteria and fungi, with prolonged antimicrobial durability. Future comparative *in vivo* testing and clinical trials of these antimicrobial catheters are needed to determine their relative contributions to reducing bloodstream infections.

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